## REMARKS

Applicants request respectfully that the allowability of the claims be reconsidered in view of the above amendments and the following remarks.

### Status of the Claims

The Examiner's Action addressed Claims 1, 7, 11, 14, 15, and 18 to 32. Claims 1, 7, 11, 14, 15, 20 to 29 and 31 were amended previously in applicant's Reply submitted on April 13, 2007. In this Supplemental Reply, Claims 1, 7, 18, 20 and 24 are amended. No claims have been added or cancelled. Accordingly, the claims pending presently for examination are Claims 1, 7, 11, 14, 15, and 18 to 32.

### Summary of Examiner Interview

Applicants gratefully acknowledge the Examiner's interview with applicants' attorney, Marc Segal, on April 26, 2007. Applicants appreciate the Examiner's helpful suggestions.

During the interview, with respect to the process claims (Claim 1 and its dependents), applicants' attorney pointed out that the claimed process differs from the prior art of record in that the lipids/polymers in the DNA complex are reacted with the reagents after already being in the DNA complex. The Examiner suggested replacing "complexed with" with "sequestered within" to make clear that the lipids/polymers are on the outside the DNA complex and thus available to be reacted with the reagents. In light of this amendment, the Examiner agreed to reconsider the allowability of the process claims.

With respect to the product claims (Claim 18 and its dependents), the Examiner suggested adding structural recitations rather than relying on product-by-process language. As explained during the interview, the claimed colloid comprising the claimed DNA complexes differs from the prior art in that it is the lipids/polymers that are "attached ionically to" the DNA that are chemically modified. As a result of the interview, applicants have amended Claim 18 to point out this structural difference. The Examiner agreed to reconsider the allowability of the product claims in view of any amendments that add structural recitations.

Discussion of the Amendments

Claim 1 has been amended to replace the phrase "complexed with" with "sequestered within" as suggested by the Examiner during the Examiner Interview along with a minor editorial amendment. This amendment is supported by original claim 1 ("sequestered DNA") and in the application as published at paragraph 11.

As suggested by the Examiner, Claim 18 has been amended to add structural recitations rather than relying on product-by-process language. In this regard, Claim 18 recites the lipids/polymers are "attached ionically to" the DNA, and that these lipids/polymers are the chemically modified reaction products of: (A) a reagent selected from the group consisting of citraconic anhydride and N-hydroxysuccinimide acetate; and (B) cationic lipids or polymers. Support for the "attached ionically to" language can be found, for example, in the published application at paragraph 35 ("...where cationic lipids or cationic lipid/neutral lipid mixtures are attached to DNA by ionic interactions.").

Editorial amendments have been made to Claims 7, 20, and 24.

No new matter has been added.

Discussion of the Invention

Applicants' invention is directed to a process for making a stable colloid that includes a complex of DNA and lipids or polymers. In the art, it is known that DNA can form complexes with lipids in which the lipids surround the DNA and sequester it. Similarly, it is known that DNA can form complexes with polymers. Because DNA is anionic, the most efficient way of forming such a complex is to use cationic lipids or cationic polymers. The cationic lipids or cationic polymers electrostatically interact with the DNA to form a complex. An undesired feature of such a complex, however, is that the complex has a cationic surface potential. In *in vivo* use, such a cationic surface potential causes anionic proteins to be attracted to the complex and causes it to be rapidly opsonized within the cell.

Given the above, it is known to modify the complex such that the cationic surface potential is reduced, removed or reversed so that the complex has a neutral or anionic surface potential to decrease opsonization of the complexes. Various methods are known in the art for accomplishing this. Such methods are described in Monahan et al. and in Trubetskoy et al. (both cited by the Examiner). In Monahan et al., N-hydroxysuccinimide ester or citraconic anhydride is used in the creation of anionic polymers which are then used to form an anionic envelope around the initial cationic envelope (the anionic polymers interact electrostatically with the cationic polymers of the initial envelope). Thus a two envelope complex is formed. Trubetskoy et al. also describes generally the formation of a second anionic envelope around the initial cationic envelope. Another method is described in Semple et al. In this method, the cationic lipid envelope is made using lipids which become anionic or neutral depending upon the pH of the surrounding environment. If the pH of the surrounding

environment is high, hydrogen atoms of the lipids which are on the exterior surface of the envelope are released, thus converting the lipids on the exterior of the envelope into anionic or neutral lipids. The lipids on the interior are not exposed to the surrounding environment and thus remain cationic and thus can continue to associate with the anionic DNA sequestered in the complex.

Applicants' development is novel and non-obvious in that, unlike Monahan et al. and Trubetskoy et al., it does not require the use of separate anionic polymers to form a second envelope around the cationic complex of DNA and cationic lipids/polymers. Rather, like Semple et al., applicants modify the exterior surface lipids/polymers of the cationic lipid/polymer-DNA complex so that the surface lipids/polymers become netural or anionic. Unlike Semple et al., however, applicants' method does not require a change in the pH of the surrounding environment. Rather, N-hydroxysuccinimide acetate (NHS acetate) or citraconic anhydride (CCA) is used to react with the cationic lipids/polymers on the surface of the complex, thus converting the exterior lipids/polymers into anionic or neutral form. The above reactions involve the addition of a chemical moiety to the lipids/polymers and not just the release of a hydrogen atom (as in Semple et al.) and as a further anionic envelope is not added (as in Monahan et al. and Trubetskoy et al.), not only is applicants' method novel and non-obvious over the prior art, but applicants' colloid is structurally different from the colloids of the prior art and novel and non-obvious thereover as well.

Discussion of the Examiner's
Section 102(e) Rejection of Claims 18 to 23 and 30 Based on Monahan et al.

The Examiner has rejected Claims 18 to 23 and 30 as being anticipated under Section 102(e) by Monahan et al. (U.S. Patent No. 6,379,966). The Examiner asserts that, absent evidence to the contrary, since Claim 18 is drawn to a stable colloid, regardless of its method of preparation, if the prior art compound reads on a process

which involves the production of a stable colloid, the claim is unpatentable even though the prior art product was made by a different process.

The novelty of Claim 18 has been reinforced by the addition of structural recitations of the type discussed with the Examiner. In particular, Claim 18 recites that the DNA complex of the claimed colloid consists essentially of DNA attached ionically to and sequestered within lipids or polymers which are chemically modified reaction products of: (A) a reagent selected from the group consisting of citraconic anhydride and N-hydroxysuccinimide acetate; and (B) cationic lipids or polymers.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference [and] . . . the elements must be arranged as required by the claim." M.P.E.P. § 2131. Here, neither Monahan et al. nor any other reference of record discloses each of the elements as arranged and required by Claim 18.

The novelty of the product claim is that the chemically modified lipid/polymers (by the claimed reagents) are ionically attached to the DNA. None of the prior art references discloses this structure. As amended, Claim 18 recites that it is the lipids/polymers that are "attached ionically to" the DNA that are chemically modified. The prior art of record does not disclose DNA complexes in which the lipids/polymers *attached to* the DNA are chemically modified. In contrast, Monahan et al. and Trubetskoy et al. disclose adding a third layer of chemically modified polymers to an existing DNA/polymer complex and, thus, the chemically modified polymers of Monahan et al. and Trubetskoy et al. are not "attached ionically to" the DNA in the complex. Rather, the chemically modified polymers of Monahan et al. and Trubetskoy et al. attach ionically to cationic polymers (not DNA) and form a third layer around the cationic polymers (second layer). (See Monahan et al. at column 23, lines 56 to 59 and

Trubestskoy et al. at paragraph 52). Semple et al. does not disclose the claimed chemically modified lipids/polymer much less disclose the DNA complex of Claim 18. Semple et al. merely shows changing the pH environment to change the charge on the lipids. (See Semple et al. Figure 1). Thus, applicant's claimed DNA complexes differ structurally from those of the prior art of record.

Claim 18 has also been amended to recite that the colloid comprises "a DNA complex . . . which *consists essentially* of DNA attached ionically to and sequestered within lipids or polymers which are chemically modified . . . ." Accordingly, applicants' claimed DNA complexes include DNA attached ionically to and sequestered within lipids/polymers, but exclude other materials that would materially affect the basic and novel characteristics of the complex. See M.P.E.P. § 2111.03. For this additional reason, the three layer approach of the DNA complexes of Monahan et al. and Trubetskoy et al. do not anticipate applicants' claimed structure.

Accordingly, applicants request respectfully that the Examiner withdraw the anticipatory rejection of Claims 18 to 23 and 30.

In view of the structural differences between the DNA complexes of Claim 18 and those of the cited references as described above, it is requested respectfully that if the Examiner issues a novelty or obviousness rejection against Claim 18, she particularly point out where each of the structural recitations of Claim 18 are disclosed in the applied references. This would enable applicant to understand the reasons for the rejection and, thus, help in accelerating prosecution of the application.

Discussion of the Examiner's Section 103(a) Rejection
Based on Semple et al., Monahan et al., and Trubetskoy et al.

The Examiner has rejected Claims 1, 7, 11, 14, 15, 18 to 23, and 28 to 32 as being rendered obvious under Section 103(a) by Semple et al. (U.S. Patent No. 6,287,591) taken with Trubetskoy et al. (US 2003/0026841) and Monahan et al. (U.S. Patent No. 6,379,966).

As amended in applicants' prior Reply and further amended herein, Claim 1 clarifies that the applicants' process involves first providing a DNA complex consisting essentially of DNA sequestered within cationic lipids or cationic polymers in which the DNA complex has a cationic surface potential, and converting the cationic surface potential of the DNA complex to a neutral or net anionic surface potential by reacting the cationic lipids or the cationic polymers *in the DNA complex* with a reagent selected from the group consisting of citraconic anhydride and N-hydroxysuccinimide acetate.

Applicants' incorporate and rely on the remarks/arguments made in response to this rejection in the Reply submitted on April 13, 2007. In summary, the prior art references cited by the Examiner do not teach or suggest all the claim recitations and there is no suggestion or motivation to combine the references as asserted by the Examiner. None of the references discloses reacting any reagent with the lipids or polymers already complexed with DNA to reduce, remove or reverse the cationic surface potential of the DNA complex.

Applicants further note that the recent Supreme Court decision, *KSR Int'l Co. v. Teleflex Inc.* (2007), supports applicants' argument that the claimed process is not obvious in view of the cited references. While the Supreme Court's decision cautioned against applying the teaching, suggestion, and motivation test in a rigid

manner, there still must be an "apparent reason to combine the known elements in the fashion claimed." *KSR*, slip op. at 14. Moreover, one of skill in the art must still see a benefit in combining the references. "The proper question to have asked was whether [one] of ordinary skill, facing the wide range of needs created by developments in the field of endeavor, would have seen a *benefit* to [combining the references]." *KSR*, slip op. at 20 (emphasis added). Here, as explained in detail in applicants' prior Reply, there is no such benefit because each reference discloses its own unique approach to addressing the problem of a cationic surface potential other than the approach recited in Claim 1. Thus, there would be no reason or benefit in combining the teachings of Semple et al., Monahan et al. and Trubetskoy et al.

Accordingly, Semple et al., Monahan et al., and Trubetskoy et al. do not render applicants' claims obvious and the Examiner's Section 103 rejection of Claims 1, 7, 11, 14, 15, 18 to 23, and 28 to 30 based thereon should be withdrawn.

Discussion of the Examiner's Indefiniteness Rejection

The Examiner rejected Claims 11, 14, 15, 21 to 23, 25 to 27, 30 and 32 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicants' incorporate and rely on the remarks/arguments made in response to this rejection in the Reply submitted on April 13, 2007.

Conclusion

In view of the foregoing amendments and remarks, applicants assert that the claims are in condition for allowance and request respectfully issuance of a Notice of

Allowance.

If any issues remain, the undersigned requests a telephone interview prior to the issuance of an action.

If any other fees are required in order to continue the prosecution of this application, the Office is authorized to charge such fees to Deposit Account 19-5425.

Respectfully submitted,

/Marc S. Segal/

Marc S. Segal
Reg. No. 40,163
Synnestvedt & Lechner LLP
1101 Market Street, Suite 2600
Philadelphia, PA 19107
Telephone: (215) 923-4466
Facsimile: (215) 923-2189